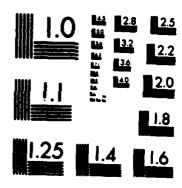
DEGENERATIVE ENZYMES(U) TEXAS A AND H UNIV COLLEGE STATION DEPT OF BIOCHEMISTRY AND BIOPHYSICS E F MEYER 30 APR 87 N00014-86-K-0662 AD-8181 765 F/G 6/1 NL UNCLASSIFIED

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Edgar F. Meyer, Jr. Texas A&M University

1. Project Goals

- A: Test the enzyme mechanism: The tetrapeptide, Pro-Ala-Pro-Tyr bound to porcine pancreatic elastase (PPE), has been studied (J. Mol. Biol. (1986) 190, 259-267). A sequal study is now in progress; "forward" binding in the active site is found.
- B. Test the enzyme mechanism: The azapeptide, Suc-Ala-Ala-Pro-azaAla, did not bind to PPE due to blockage at the S4 site. Further study will be made with a shortened azapeptide; this should help capture a reaction intermediate.
- C. Inhibitor binding: Several studies of newer isocoumarins have been made using low-resolution diffractometer as well as high-resolution film data. In all cases either the PPE active site was "empty" or else the low electron density indicated statistical disorder. Prof. Powers has found an approximate 50:50 distribution of two competing reactions (nucleophile = His 57 or OH-) over a broad pH range (Biochem. (1985) 24, 7200-7213). Some inhibitors are too insoluble in aqueous buffers to yield complexes, in the face of competing reactions (e.g., hydrolysis).
- D. Inhibitor binding: Insufficient resources (data collection, manpower) have kept us from studying 3-benzyl-yne-enol-butyrolactone.
- E. Inhibitor binding: A low-resolution data set of the ketoester showed no binding, presumably because of blockage at the S4 site. A shorter ketoester was made available to us very recently. Synthesis of a shorter inhibitor is now in progress.
- F. The structure of human leucocyte elastase (HLE) has been solved (EMBO Journal (1986) 5, 2453-2458); preliminary structural data are being used to study differential binding of inhibitors between PPE and HLE.



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Synopsisa) List of publications

"Computer Aided Prediction and Evaluation of the Tertiary Structure of Rat Elastase II", Gail M. Carlson, Raymond J. MacDonald, and Edgar F. Meyer, Jr., J. Theoretical Biology (1986) 119, 107-124.

"Structure of the Product of Acetyl-Ala-Pro-Ala with Porcine Pancreatic Elastase at 1.65A Resolution", E.F. Meyer, Jr., R. Radhakrishnan, G.M. Cole, and L.G. Presta, J. Mol. Biol. (1986) 189, 533-539.

"Stereochemistry of Binding of the Tetrapeptide Acetyl-Pro-Ala-Pro-Tyr-NH2 to Porcine Pancreatic Elastase...", M.C. Clore, A. Gorenborn, G. Carlson and E.F. Meyer, Jr., J. Mol. Biol. (1986) 190, 259-267.

"Intermolecular Enzyme-Ligand Animation in the Active Site of Porcine Pancreatic Elastase with Acetyl-Alaine-Proline-Alanine by means of Molecular Dynamics Calculations", T. Fujita, S.M. Swanson, and E.F. Meyer, Jr., J. Mol. Graphics (1986) 4, 208-212.

"Prediction of Protein-Ligand Interactions: The Complex of Porcine Pancreatic Elastase with a Valine-Derived Denzoxazinone", L.G. Presta and E.F. Meyer, Jr, (1986), Biopolymers, submitted.

"X-ray Crystal Structure of the Complex of Human Leucocyte Elastase (PMN Elastase) and the Third Domain of the Turkey Ovomucoid Inhibitor", W. Bode, An-Zhi Wei, R. Huber, E. Meyer, J. Travis, and S. Neumann, EMBO Journal (1986) 5, 2453-2358.

"The Study and Design of Specific Inhibitors to Elastase", E. Meyer and W. Bode, in "Progr ess in QSAR; QSAR in Drug Design and Toxicology, 1987, 247-254, D. Hadzi and B. Jerman-Blazic, Eds., Elsevier, Amsterdam.

"A Structure: Function Study of Receptor + Substrate Interactions Derived from High-Resolution X-ray Crystallography" in "Molecular Structure: Chemical Reactivity and Biological Activity", J. Stezowski, ed., Oxford University Press, in press.

c) Major Presentations

"A Structure-Functionk Study of Receptor + Substrate Interactions Derived from High-Resolution X-ray Crystallography", presented at an International Symposium in Beijing, China, September 15-21, 1986.

"The Study and Design of Specific Inhibitors to Elastase", presented at the 6th European Symposium on Quantitative Structure-Activity Relationships, Portorose, Yugoslavia, September 22-26, 1986.

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